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(54) Title: NEW PROCESS			
(57) Abstract <p>The invention provides a process for preparing essentially crystalline particles containing a substance in solvated form, by dissolving the substance in a first solvent, introducing the solution and a supercritical or subcritical fluid into an apparatus, wherein the fluid contains an anti-solvent and a second solvent, which is water. Preferably, the anti-solvent is carbon dioxide which is totally saturated with the second solvent, which is water. The invention further provides formulations comprising particles produced according to the present process containing one or more pharmacologically active substances and one or more pharmaceutically acceptable excipients, use of said formulations in the treatment of an allergic and/or inflammatory condition of the nose or lungs and methods for treatment of such conditions.-</p>			

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## NEW PROCESS

### FIELD OF THE INVENTION

5 The present invention is directed to a process for preparing essentially crystalline particles containing a substance in a solvated form, the resulting particles being useful e.g. for oral or nasal inhalation.

### BACKGROUND OF THE INVENTION

10

The increasing production and use of fine powders in the pharmaceutical industry has highlighted the need for reliable methods for assessing their physicochemical and technical handling. Particles obtained by spray drying, freeze drying, rapid solvent quenching or from controlled precipitation will often be in an amorphous state or in a meta-stable crystalline form. For crystalline substances, a diminution operation, e.g. micronization, will  
15 give particles with amorphous regions.

The usefulness of amorphous and/or meta-stable crystalline particles is limited due to their thermodynamic instability. For example, such particles tend to fuse in the presence of  
20 moisture, thereby forming hard agglomerates which are difficult to break up. Furthermore, amorphous and/or meta-stable crystalline particles exhibit larger batch-to-batch variations as regards bulk density than do well-defined crystalline particles. This may cause problems e.g. in inhalers for treating respiratory disorders, due to lower dosing accuracy.

25 It is therefore desirable to produce crystalline or at least essentially crystalline particles, which exhibit a good dosing accuracy and storage stability.

Methods to convert the amorphous or meta-stable crystalline particles into crystalline particles are known. Examples are disclosed in US 5,709,884 and US 5,562,923 both to  
30 Astra AB of Sweden.

The known methods to produce crystalline particles are, however, often time consuming requiring substantial space. Therefore, there is a need for a more efficient technique for producing crystalline particles with a high shelf life.

## SUMMARY OF THE INVENTION

The object of the present invention is to provide a process for preparing essentially crystalline particles containing a substance in a solvated form, comprising dissolving the substance in a first solvent, introducing into an apparatus under supercritical or subcritical conditions the solution containing the substance with an anti-solvent and a second solvent, which is water and recovering the essentially crystalline particles formed containing the substance in a solvated form.

According to a preferred embodiment of the invention, the anti-solvent is carbon dioxide.

According to another preferred embodiment, the relative solvent saturation of the anti-solvent lies in the range of from 15% up to 50% of total solvent saturation at the prevailing pressure and temperature.

## DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to a process for preparing essentially crystalline particles containing a substance in a solvated form, comprising

- (a) dissolving the substance in a first solvent;
- (b) introducing into an apparatus the solution containing the substance together with a supercritical or subcritical fluid comprising an anti-solvent and a second solvent which is water, and
- (c) recovering the essentially crystalline particles formed.

The inventors of the present process, have surprisingly found that by applying a supercritical or subcritical fluid comprising an anti-solvent and a second solvent, which is water to a solution containing the substance at issue, essentially crystalline particles can be obtained. This is especially true if the particles are post-conditioned with the supercritical or subcritical fluid.

The process of the present invention can be performed in accordance with fluid gas anti-solvent techniques, wherein fluid gas includes material in its supercritical, near critical and subcritical states as well as compressed gases. Suitable fluid gas anti-solvent techniques, include but are not limited to, GAS (gas anti-solvent precipitation), a modified version of the GAS technique known as SEDS (solution enhanced dispersion by supercritical fluid), ASES (aerosol solvent extraction system), SAS (supercritical anti-solvent) and PCA (precipitation with compressed fluid anti-solvent). Preferably use is made of the SEDS technique.

The traditional SEDS technique employs an apparatus comprising a particle-forming vessel with means for controlling the temperature and pressure of said vessel, together with a means for co-introduction into said vessel of a supercritical or subcritical fluid and a vehicle containing at least one substance in solution or suspension, such that dispersion and extraction of the vehicle occur simultaneously by the action of the fluid.

To make the present invention work, especially if it is performed in accordance with the SEDS technique, the following criteria apply to the combination of first solvent, second solvent, anti-solvent, and the substance at issue:

- i) the substance at issue must be essentially soluble in the first solvent,
- ii) the first solvent must be miscible with the anti-solvent, e.g. carbon dioxide,
- iii) the second solvent must be miscible with the anti-solvent,
- iv) the substance at issue should be insoluble in the anti-solvent,
- v) the amount of second solvent in the anti-solvent must not exceed that needed for saturating the supercritical or subcritical anti-solvent.

The latter criterion is essential for avoiding formation of a two-phase system containing supercritical solvent-saturated anti-solvent, e.g. water-saturated carbon dioxide, and a liquid phase containing e.g. water, solvent and dissolved active substance.

5

In the SEDS technique, the substance at issue is dissolved in the solvent and co-introduced into an apparatus via a nozzle having at least two channels, one channel for a solvent and one channel for an anti-solvent i.e. the supercritical or subcritical fluid. Mixing and dispersion occur at the spot where the fluids meet. The supercritical fluid dissolves the solvent but not the substance since the substance must be insoluble in the anti-solvent. Therefore,  
10 the substance will precipitate as particles with a suitable size.

15

A suitable apparatus for the SEDS process is described in WO 95/01221. The SEDS technique is further described in WO 96/00610. WO 95/01221 and WO 96/00610 (both to the University of Bradford, GB), are hereby incorporated by reference.

20

A "supercritical fluid" is a fluid at or above its critical pressure ( $P_c$ ) and critical temperature  $T_c$ ) simultaneously. Supercritical fluids also encompass "near supercritical fluids", which are above but close to its critical pressure ( $P_c$ ) and critical temperature  $T_c$ ) simultaneously.  
A "subcritical fluid" is above its critical pressure ( $P_c$ ) and close to its critical temperature ( $T_c$ ).

25

The anti-solvent is suitably one or more of carbon dioxide, nitrous oxide, sulfur hexafluoride, ethane, ethylene, propane, n-pentane, xenon, trifluoromethane, chlorotrifluoromethane, a fluorocarbon compound, a chlorofluorocarbon compound, nitrogen, or water.  
The anti-solvent is preferably carbon dioxide.

In the present invention, the supercritical or subcritical fluid contains an anti-solvent and a second solvent, which is water, is miscible with said anti-solvent.

30

Immediately before the supercritical or subcritical fluid is introduced in the particle-forming vessel, the relative solvent saturation of the anti-solvent may be in the range of from about 50% up to 100%, i.e. total, solvent saturation at the prevailing pressure and temperature. Immediately before treating the particles in the conditioning vessel, the  
5 relative solvent saturation of the anti-solvent is suitably in the range of from 70% up to 100%, preferably from 90% up to 100%, and more preferably from 95 % up to 100% of total solvent saturation at the prevailing pressure and temperature.

A particularly preferred combination of anti-solvent and solvent is carbon dioxide and  
10 water, advantageously when the relative water-saturated supercritical carbon dioxide (RWSSC) lies in the range of from about 50% up to 100%, i.e. total saturation, especially when the RWSSC lies in the range of from 90% up to 100%, and more especially when the RWSSC lies in the range of from 95% up to 100% of total solvent saturation at the prevailing pressure and temperature.

15

The flow rate ratio between dry and totally solvent saturated anti-solvent may be in the range of from about 10:1 to about 1:10, suitably from 8:1 to 1:5, preferably from 6:1 to 1:1, when preparing a supercritical or subcritical fluid which is not totally solvent saturated.

20 The particles produced according to the present process, may be subsequently treated with a dry anti-solvent in a supercritical or subcritical state for obtaining particularly dry particles. It is however, preferred that use is made of fluid containing an anti-solvent, especially carbon dioxide, and a second solvent, which is water, also for subsequent conditioning of the particles formed, since this ensures that the substance in solvated form will mature into,  
25 and remain as, essentially crystalline particles. The supercritical or subcritical fluid containing an anti-solvent and the second solvent, may be totally saturated with the solvent or exhibit a relative solvent saturation of the anti-solvent in the range of from about 50% up to 100%, i.e. total saturation, suitably in the range of from 90% up to 100%, and preferably in the range of from 95% up to 100% of total solvent saturation at the prevailing  
30 pressure and temperature.

The particles of the invention may contain one or more pharmacologically active substance(s) in a solvated form and/or one or more pharmaceutically acceptable excipients in a solvated form, both intended for use in mammals, preferably human beings.

The solvate is a hydrate, such as a monohydrate, dihydrate or trihydrate.

The first solvent used for dissolving the substance at issue, can be one or more organic solvents, optionally in mixture with one or more polar solvents such as water. The solvent may be a lower alkyl alcohol, such as methanol, ethanol, n-propanol, isopropanol, n-butanol, iso-butanol, sec-butanol or tert-butanol, an aldehyde, a ketone, such as acetone, an ester, dimethylsulfoxide (DMSO), or any mixture of any of these.

The pharmacologically active substance can be selected from the group consisting of solvates of  $\beta$  agonists, including short acting and long acting  $\beta 1$  and  $\beta 2$  agonists, glucocorticosteroids, anticholinergics, leukotriene antagonists and proteins and peptides, especially inhalable proteins and peptides, and any mixture thereof, especially a solvate of a  $\beta$  agonist and a glucocorticosteroid.

$\beta$  agonists for use in the present invention include, without limitation, solvates of formoterol, salbutamol, rimiterol, fenoterol, reproterol, pirbuterol, bitolterol, salmeterol, clenbuterol, procaterol, broxaterol, picumeterol, mabuterol, terbutaline, isoprenaline, orciprenaline, adrenaline, and pharmaceutically acceptable esters, acetals, and salts, and any mixture thereof. Suitably, use is made of solvates of formoterol, or any pharmaceutically acceptable salt thereof.

Suitable pharmaceutically acceptable salts of formoterol include acid addition salts derived from inorganic and organic acids, for example the chloride, bromide, sulfate, phosphate, maleate, fumarate, tartrate, citrate, benzoate, 4-methoxybenzoate, 2- or 4-hydroxybenzoate, 4-chlorobenzoate, p-toluenesulphonate, methanesulphonate, ascorbate, acetate, succinate,



lactate, glutarate, gluconate, tricarballoylate, hydroxynaphthalene-carboxylate or oleate salts or solvates thereof. The pharmacologically active substance is preferably a solvate of formoterol fumarate, and most preferably formoterol fumarate dihydrate.

- 5 The glucocorticosteroid, if used in the invention, is preferably an anti-inflammatory glucocorticosteroid, e.g. for use in nasal or oral inhalation, or for use in the treatment of intestinal diseases such as inflammatory bowel diseases (IBD), Crohn's disease or ulcerative colitis. Examples of glucocorticosteroids which may be used in the present invention include any solvate of betamethasone, fluticasone (e.g. as propionate), budesonide,
- 10 tipredane, dexamethasone, beclomethasone (e.g. as dipropionate), prednisolone, fluocinolone (e.g. as acetonide), triamcinolone (e.g. as acetonide), mometasone (e.g. as furoate), rofleponide, flumethasone, flunisolide, ciclesonide, deflazacort, cortivazol, 16 $\alpha$ ,17 $\alpha$ -butylidenedioxy-6 $\alpha$ ,9 $\alpha$ -difluoro-11 $\beta$ ,21-dihydroxy-pregna-1,4-diene-3,20-dione; 6 $\alpha$ ,9 $\alpha$ -difluoro-11 $\beta$ -hydroxy-16 $\alpha$ ,17 $\alpha$ -butylidenedioxy-17 $\beta$ -methylthio-androsta-4-ene-3-
- 15 one; 16 $\alpha$ ,17 $\alpha$ -butylidenedioxy-6 $\alpha$ ,9 $\alpha$ -difluoro-11 $\beta$ -hydroxy-3-oxo-androsta-1,4-diene-17 $\beta$ -carbothioic acid S-methyl ester; methyl 9 $\alpha$ -chloro-6 $\alpha$ -fluoro-11 $\beta$ -hydroxy-16 $\alpha$ -methyl-3-oxo-17 $\alpha$ -propionyloxy-androsta-1,4-diene-17 $\alpha$ -carboxylate; 6 $\alpha$ ,9 $\alpha$ -difluoro-11 $\beta$ -hydroxy-16 $\alpha$ -methyl-3-oxo-17 $\alpha$ -propionyloxy-androsta-1,4-diene-17 $\beta$ -carbothioic acid S-(2-oxo-tetrahydrofuran-3-yl) ester; optionally in their pure isomeric forms (where such
- 20 forms exist), any solvate of any pharmaceutically acceptable ester, acetal or salt thereof, and any mixture of any of these.

- Pharmaceutically acceptable excipients are e.g. carriers, additives and diluents, including antioxidants. Suitable pharmaceutically acceptable excipients include, without limitation ,
- 25 solvates of one or more natural or synthetic carbohydrate, such as a monosaccharides, disaccharides, trisaccharides, oligosaccharides, polysaccharides and polyols, and/or in the form of their pharmaceutically acceptable esters, acetals, or salts (where such derivatives exist). Examples of naturally occurring monosaccharides include glucose, fructose and galactose. Examples of naturally occurring disaccharides include sucrose (saccharose),
- 30 trehalose, maltose, cellobiose and lactose. The disaccharide is preferably lactose, more

preferably lactose monohydrate. Examples of naturally occurring trisaccharides include raffinose and melezitose. The polysaccharide may be cellulose, starch, dextrans or dextran, or chemical derivatives of any of these. The cellulose derivative is suitably a cellulose ether such as ethylcellulose (EC), ethylmethylcellulose (EMC), hydroxyethylcellulose (HEC),  
5 ethylhydroxymethylcellulose (EHMC), ethylhydroxyethylcellulose (EHEC), methylcellulose (MC), hydroxymethylcellulose (HMC), hydroxypropylcellulose (HPC), hydroxypropylmethylcellulose (HPMC) and carboxymethylcellulose (CMC), e.g. the sodium salt thereof. The polyol is preferably a sugar alcohol, which can be obtained by reducing various monosaccharides. For example, sorbitol and mannitol may be obtained by reducing  
10 glucose and mannose, respectively.

The pharmacologically active substance or substances may be premixed with one or more pharmaceutically acceptable excipients before the process of the invention is applied. This is especially advantageous if the active substance is highly potent. It is, however, also  
15 possible to prepare crystalline particles containing an active substance according to the present invention and mix them with suitable excipient(s) afterwards. In this case, the excipient particles may also be produced according to the present invention, using e.g. the SEDS technique, or may be produced by some other suitable technique. It is further possible to prepare crystalline particles containing one or more excipient(s) according to  
20 the present invention and mix them with particles containing one or more active substances afterwards. In this case, the particles containing an active substance may also be produced according to the present invention, or may be produced by some other suitable technique.

When the particles produced contain a pharmacologically active substance the particles are  
25 suitably in a finely divided form, preferably having a mass median diameter (MMD) (as measured using a Coulter counter) of less than about 20  $\mu\text{m}$ , more preferably of less than 10  $\mu\text{m}$ , and most preferably with an MMD in the range of from 1 to 6  $\mu\text{m}$ . The particles may alternatively be in an ultra fine form, e.g. having an MMD of less than 1.0  $\mu\text{m}$ .

When the particles produced contain one or more pharmaceutically acceptable excipient the particles may have a mass median diameter (MMD) (as measured using a Coulter counter) of less than about 100  $\mu\text{m}$ , suitably of less than 50  $\mu\text{m}$ , preferably with an MMD of less than 20  $\mu\text{m}$ , and more preferably with an MMD of less than 10  $\mu\text{m}$ .

5

The present process is carried out under supercritical or subcritical conditions. The precise conditions of operation are dependent e.g. upon the choice of anti-solvent. Table 1, lists the critical pressure ( $P_c$ ) and critical temperature ( $T_c$ ) for some anti-solvents.

10

TABLE 1

Anti-solvent	$P_c$ (bar)	$T_c$ ( $^{\circ}\text{C}$ )
Carbon dioxide	74	31
Nitrous oxide	72	36
Sulfur hexafluoride	37	45
Ethane	48	32

TABLE 1 (cont.)

Ethylene	51	10
Xenon	58	16
Trifluoromethane	47	26
Chlorotrifluoromethane	39	29

In practice, it may be preferable to maintain the pressure inside the substance vessel substantially above the relevant  $P_c$  whilst the temperature is only slightly above the  $T_c$ . Generally, therefore, the pressure may be in the range of from about 10 up to about 300 bar higher than the relevant  $P_c$ , suitably in the range of from 20 up to 200 bar higher, and preferably be in the range of from 30 up to 100 bar higher than the relevant  $P_c$ . Generally, also, the temperature may be in the range of from about 5 up to about 50°C above the relevant  $T_c$ , suitably in the range of from 10 up to 40°C above, and preferably in the range of from 15 up to 30°C above the relevant  $T_c$ .

With carbon dioxide, the pressure may be in the range of from about 80 up to about 400 bar, suitably in the range of from 100 to 250 bar, preferably in the range of from 110 to 150 bar whilst the temperature may be in the range of from about 35 up to about 80°C, suitably in the range of from 40 up to 70°C, preferably in the range of from 45 up to 60°C.

The solution of dissolved substance and the supercritical or subcritical fluid containing an anti-solvent and a solvent should be pumped through the particle-forming vessel for a period of time selected such that the desired particle characteristics are obtained.

The period of time can be regulated by altering the pressure, temperature and/or flow rate.

The solution and supercritical or subcritical fluid containing an anti-solvent and a solvent can be pumped for a period of time in the range of from about 5 min up to about 48 hours, suitably from 15 min up to 24 hours, preferably from 30 min up to 12 hours.

After the formation of particles in the particle-forming vessel, it is suitable to condition the particles formed by circulating the fluid containing an anti-solvent and a second solvent for an additional period of time. The anti-solvent can be circulated for an additional period of time in the range of from about 1 min up to about 12 hours, suitably from 5 min up to 6  
5 hours, preferably from 10 min up to 3 hours.

Conveniently, the present process is carried out as a one-way process, i.e. the supercritical or subcritical fluid passes the conditioning vessel only once. It is, however, possible to recirculate the supercritical or subcritical fluid after essentially restoring the initial relative  
10 or total solvent saturation value before the fluid reenters the conditioning vessel.

An apparatus suitable for use as a conditioning vessel in the present process, must be able to withstand the pressure and temperature prevailing at the preselected supercritical or subcritical condition. Furthermore, the apparatus must be able to withstand the impact of  
15 the anti-solvent/solvent mixture at issue under supercritical or subcritical conditions.

According to the invention there is also provided a pharmaceutical formulation comprising one or more pharmacologically active substance(s) produced according to the present invention and one or more pharmaceutically acceptable excipient(s). Examples of such  
20 excipients include carriers such as carbohydrates e.g. in a solvated form, additives such as antioxidants, and diluents. The active substance(s) are preferably selected from the group consisting of solvates of  $\beta$  agonists, glucocorticosteroids, anticholinergics, leukotriene antagonists, proteins and peptides, and any mixture thereof.

25 The invention further provides particles produced according to the present process containing one or more pharmacologically active substance(s) selected from the group consisting of solvates of  $\beta$  agonists, glucocorticosteroids, anticholinergics, leukotriene antagonists, proteins and peptides, mixed with one or more pharmaceutically acceptable excipient(s), for use in the treatment of a respiratory disorder such as an allergic and/or  
30 inflammatory condition of the nose or lungs, e.g. chronic obstructive pulmonary disease

(COPD), rhinitis or asthma, or for use in the treatment of intestinal diseases such as inflammatory bowel diseases (IBD), Crohn's disease or ulcerative colitis.

The invention further provides a method for treatment of an allergic and/or inflammatory condition of the nose or lungs by administering to a mammal, especially a human being, suffering from such a condition a therapeutically effective amount of a formulation containing one or more pharmacologically active substance(s) selected from solvates of  $\beta$  agonists, glucocorticosteroids, anticholinergics, leukotriene antagonists, proteins and peptides, mixed with one or more pharmaceutically acceptable excipient(s). More specifically, the invention provides a method for treatment of chronic obstructive pulmonary disease (COPD), rhinitis, asthma or other allergic and/or inflammatory conditions, or for treatment of intestinal diseases such as inflammatory bowel diseases (IBD), Crohn's disease or ulcerative colitis by administering to a mammal, especially a human being, suffering from such a condition a therapeutically effective amount of a formulation containing one or more pharmacologically active substance(s) selected from solvates of  $\beta$  agonists, glucocorticosteroids, anticholinergics, leukotriene antagonists, proteins and peptides.

The invention will be illustrated by the following examples which are not intended to limit the scope of the invention.

## EXAMPLES

### COMPARATIVE EXAMPLE 1

25

Several experiments were performed with a SEDS apparatus wherein dry carbon dioxide was used as the anti-solvent during the whole process for crystallizing formoterol fumarate dihydrate.

Various solvents were utilized, including methanol, ethanol, isopropanol, acetone, acetonitrile, and dimethylsulfoxide (DMSO) as well as solvent mixtures such as water/methanol water/isopropanol, water/acetone. The pressure inside the particle-forming vessel was varied between 90 to 300 bar, and the temperature inside the oven was varied between 32 to 75°C.

When organic solvents such as alcohols or alcohol-water mixtures were used to crystallize formoterol fumarate dihydrate using the conventional SEDS technique with a dry anti-solvent, it resulted in the formation of agglomerated particles, and amorphous powders containing formoterol fumarate dihydrate. No crystalline formoterol fumarate dihydrate was obtained in these experiments.

#### COMPARATIVE EXAMPLE 2

A further experiment was performed with the SEDS apparatus used in Comparative Example 1, wherein dry carbon dioxide was used as the anti-solvent during the whole process.

0.370 g of formoterol fumarate dihydrate was dissolved in 17 ml of a mixture containing 1% water and 99% methanol. The concentration was thus 2.0 % (w/v). The pressure and temperature inside the particle-forming vessel were 150 bar and 40°C, respectively. The nozzle opening was 0.2 mm and dry carbon dioxide was used as the anti-solvent. The flow rate of carbon dioxide pumped through the nozzle was 18.0 ml/min while that of the solution was 0.3 ml/min. The solution was pumped for 60 min and 30 mg of substance was obtained.

X- ray analysis revealed that the substance was totally amorphous.

## EXAMPLE 3

An experiment was performed according to the invention using a modified SEDS apparatus, wherein totally water-saturated carbon dioxide was used as the anti-solvent for crystallizing formoterol fumarate dihydrate. The same anti-solvent was used for flushing the particle-forming vessel for a defined period of time after precipitation of the solvate. The system was subsequently rinsed with dry carbon dioxide.

Totally water-saturated carbon dioxide was used as anti-solvent and the obtained substance was conditioned using totally water-saturated carbon dioxide. 0.387 g formoterol fumarate dihydrate was dissolved in 19 ml methanol (the concentration was 2.0%w/v). The pressure and temperature inside the particle-formation vessel were 150 bar and 40°C, respectively. The flow rate of carbon dioxide pumped through the nozzle was 18.0 ml/min while that of the solution was 0.3 ml/min. The nozzle opening was 0.2 mm. The solution was pumped into the particle-formation vessel for 60 min and 0.290 g formoterol fumarate dihydrate was obtained. In this experiment totally water-saturated carbon dioxide was flushed through the particle-forming vessel after the end of the run. A rinsing period followed, wherein dry carbon dioxide equivalent to two volumes of the vessel was used.

The obtained powder was crystalline according to the X-ray analysis and its diffractogram corresponded to the dihydrate form of formoterol fumarate.



## CLAIMS

1. A process for preparation of essentially crystalline particles containing a substance in a solvated form, comprising
  - 5 (a) dissolving the substance in a first solvent;
  - (b) introducing into an apparatus the solution containing the substance together with a supercritical or subcritical fluid comprising an anti-solvent and a second solvent, which is water and
  - (c) recovering the essentially crystalline particles formed.
- 10 2. The process according to claim 1, wherein the anti-solvent is carbon dioxide.
3. The process according to claim 1 or 2, wherein the temperature lies in the range of from about 5 up to about 50°C above the critical temperature ( $T_c$ ) of the anti-solvent,  
15 preferably in the range of from 15 up to 30°C above the  $T_c$ .
4. The process according to any previous claim, wherein the pressure lies in the range of from about 10 up to about 300 bar higher than the critical pressure ( $P_c$ ) of the anti-solvent, preferably be in the range of from 30 up to 100 bar higher than the  $P_c$ .
- 20 5. The process according to any previous claim, wherein the first solvent is an organic solvent, such as a lower alkyl alcohol, aldehyde, ketone, ester, ether, or any mixture thereof.
- 25 6. The process according to claim 5, wherein the lower alkyl alcohol is selected from the group consisting of methanol, ethanol, n-propanol, isopropanol, n-butanol, isobutanol, sec-butanol, tert-butanol, and any mixture thereof.

7. The process according to any previous claim, wherein before the supercritical or subcritical fluid is introduced in the particle-forming vessel the fluid is saturated with the solvent in the range of from about 50% up to 100%, preferably from 90% up to 100% of total solvent-saturation at the prevailing pressure and temperature.
- 5 8. The process according to any previous claim, wherein the flow rate ratio between dry and totally solvent saturated anti-solvent lies in the range of from about 10:1 to about 1:10, preferably from 6:1 to 1:1.
- 10 9. The process according to any previous claim, wherein the particles produced have a mass median diameter (MMD) of less than about 20  $\mu\text{m}$ , preferably less than 10  $\mu\text{m}$ .
10. The process according to any previous claim, wherein the substance in a solvated form is a pharmacologically active substance selected from the group consisting of any  
15 solvate of  $\beta$  agonists, glucocorticosteroids, anticholinergics, leukotriene antagonists, proteins and peptides, and any mixture thereof.
11. The process according to claim 10, wherein the  $\beta$  agonist in a solvated form is selected from the group consisting of solvates of formoterol, salbutamol, rimiterol,  
20 fenoterol, reproterol, pirbuterol, bitolterol, salmeterol, clenbuterol, procaterol, broxaterol, picumeterol, mabuterol, terbutaline, isoprenaline, orciprenaline, adrenaline, and pharmaceutically acceptable esters, acetals, and salts of any of these, and any mixture thereof.
12. The process according to claim 10 or 11, wherein the pharmacologically active  
25 substance in a solvated form is a hydrate, such as a monohydrate, dihydrate, or trihydrate.
13. The process according to claim 11 or 12, wherein the pharmacologically active substance in a solvated form is formoterol fumarate dihydrate.

14. The process according to any one of claims 1-9, wherein the substance in a solvated form is a pharmaceutically acceptable carbohydrate selected from the group consisting of solvates of monosaccharides, disaccharides, trisaccharides, oligosaccharides, polysaccharides and polyols, and any mixture thereof.

15. The process according to claim 14, wherein the carbohydrate in a solvated form is a hydrate, such as a monohydrate, dihydrate, or trihydrate.

16. The process according to claim 14 or 15, wherein the carbohydrate is lactose monohydrate.

17. A pharmaceutical formulation comprising one or more pharmacologically active substance in a solvated form produced according to any one of claims 1-13 and one or more pharmaceutically acceptable excipient(s).

18. The pharmaceutical formulation according to claim 17, wherein the pharmacologically active substance(s) in a solvated form are selected from the group consisting of solvates of  $\beta$  agonists, glucocorticosteroids, anticholinergics, leukotriene antagonists, proteins and peptides, and any mixture thereof.

19. The pharmaceutical formulation according to claim 17 or 18, wherein the  $\beta$  agonist in a solvated form is selected from the group consisting of solvates of formoterol, salbutamol, rimiterol, fenoterol, reproterol, pirbuterol, bitolterol, salmeterol, clenbuterol, procaterol, broxaterol, picumeterol, mabuterol, terbutaline, isoprenaline, orciprenaline, adrenaline, and pharmaceutically acceptable esters, acetals, and salts of any of these, and any mixture thereof.

20. The pharmaceutical formulation according to any one of claims 17-19, wherein the pharmacologically active substance in a solvated form is a hydrate, such as a monohydrate, dihydrate, or trihydrate.

21. The pharmaceutical formulation according to claim 20, wherein the pharmacologically active substance in a solvated form is formoterol fumarate dihydrate.
- 5 22. The pharmaceutical formulation according to any one of claims 17-21, wherein the pharmaceutically acceptable excipient is a carbohydrate selected from the group consisting of monosaccharides, disaccharides, trisaccharides, oligosaccharides, polysaccharides, polyols, and pharmaceutically acceptable solvates of any of these, and any mixture thereof.
- 10 23. The pharmaceutical formulation according to claim 22, wherein the carbohydrate is in a solvated form, preferably as a hydrate, such as a monohydrate, dihydrate, or trihydrate.
24. The pharmaceutical formulation according to claim 22 or 23, wherein the carbohydrate is lactose monohydrate.
- 15 25. The pharmaceutical formulation according to any one of claims 17-24, wherein the particles produced have a mass median diameter (MMD) of less than about 20  $\mu\text{m}$ , preferably less than 10  $\mu\text{m}$ .
- 20 26. Use of the formulation according to any one of claims 17-25 in the manufacture of a medicament for use in the treatment of an allergic condition and/or inflammatory condition of the nose or lungs.
27. Use of the formulation according to any one of claims 17-25 in the manufacture of  
25 a medicament for use in the treatment of chronic obstructive pulmonary disease (COPD), rhinitis or asthma.
28. Method for treatment of an allergic and/or inflammatory condition of the nose or lungs comprising administering to a mammal suffering from such a condition a therapeutically effective amount of the formulation according to any one of claims 17-25.  
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29. Method for treatment of chronic obstructive pulmonary disease (COPD), rhinitis or asthma comprising administering to a mammal suffering from such a condition a therapeutically effective amount of the formulation according to any one of claims 17-25.

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30. Method for treatment of inflammatory bowel diseases (IBD), Crohn's disease or ulcerative colitis comprising administering to a mammal suffering from such a condition a therapeutically effective amount of the formulation according to any one of claims 17-25.

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 99/02153

## A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61K 9/14, A61K 31/00, A61K 38/00

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI, PATENT ABSTRACTS OF JAPAN, EMBASE, MEDLINE, CASEARCH

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 9501221 A1 (UNIVERSITY OF BRADFORD), 12 January 1995 (12.01.95), see especially page 13; lines 6-24; page 14, lines 15-22	1-29
A	--	30
Y	EP 0677332 A2 (SIEVERS, ROBERT, E.), 18 October 1995 (18.10.95), page 5, line 37 - line 42	
	-- -----	

☐ Further documents are listed in the continuation of Box C.☒ See patent family annex.

## \* Special categories of cited documents:

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

\*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

\*X\* document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

\*Y\* document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

\*&\* document member of the same patent family

Date of the actual completion of the international search

28 March 2000

Date of mailing of the international search report

05-04-2000

Name and mailing address of the ISA/  
Swedish Patent Office  
Box 5055, S-102 42 STOCKHOLM  
Facsimile No. +46 8 666 02 86

Authorized officer

Anneli Jönsson/EÖ  
Telephone No. +46 8 782 25 00

# INTERNATIONAL SEARCH REPORT

International application No.  
**PCT/SE 99/02153**

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: **28-30**  
because they relate to subject matter not required to be searched by this Authority, namely:  
**see next sheet**
2. ☐ Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

### Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.  
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.  
PCT/SE 99/02153

Claims 28-30 relate to methods of treatment of the human or animal body by surgery or by therapy/diagnostic methods practised on the human or animal body/Rule 39.1(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.



# INTERNATIONAL SEARCH REPORT

Information on patent family members

02/12/99

International application No.

PCT/SE 99/02153

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9501221 A1	12/01/95	AT 174530 T	15/01/99
		AU 677345 B	17/04/97
		AU 7007194 A	24/01/95
		CA 2166301 A	12/01/95
		DE 69415320 D,T	24/06/99
		EP 0706421 A,B	17/04/96
		SE 0706421 T3	
		ES 2128564 T	16/05/99
		GR 3029612 T	30/06/99
		JP 8511987 T	17/12/96
		NZ 267697 A	26/05/97
		SG 47392 A	17/04/98
		US 5851453 A	22/12/98
EP 0677332 A2	18/10/95	US 5639441 A	17/06/97